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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,962	12/31/2003	Chandrika Govardhan	ALTUS-4	2164

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EXAMINER	
NOAKES, SUZANNE MARIE	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/749,962	GOVARDHAN ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *1-3,5,6,11-16 and 23-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *4,7-10 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/11/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 4, claims 4, 7-10 and 17(d)-22 in the reply filed on 29 June 2006 is acknowledged. The traversal is on the ground(s) that Applicants feel the 10-way restriction is not justified because there would be no undue search burden for the examiner to search all of the different crystals at once. This is not found persuasive because clearly each different crystal possesses its own unique composition which is required to make each human growth hormone crystal wherein said unique composition does in fact give rise to unique crystal morphologies. Furthermore, the search for polyarginine in one crystal will not give rise to a search, for example, for calcium. Thus, the requirement is still deemed proper and is therefore made FINAL.

Status of the Claims

2. The amendment to the claims filed 29 June 2006 is acknowledged. Claims 1-59 are pending; claims 1-3, 5, 6, 11-16 and 23-59 are withdrawn at this time from further consideration as they are drawn to non-elected subject matter. Claims 4, 7-10 and 17-22 are subject to examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 11 January 2005 has been considered by the examiner. See initialed and signed PTO-1449.

Specification

4. The use of the trademarks Nutropin Depot®, Albutropin™ and Infitropin CR™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on p. 4, lines 8, 19 and 24 and on p. 18 line 14. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. N.B. Removal of http:// is sufficient to overcome this objection.

6. The disclosure is objected to because of the following informalities: It is noted that there are 26 Tables in the specification, however, there is no Table 15. Thus, the Tables should be renumbered to end in Table 25.

Appropriate correction is required.

Claim Objections

7. Claims 7-9 are objected to because of the following informalities: the term "*in vivo*" should be italicized in each instance. Appropriate correction is required.

8. Claims 4, 7-10 and 17-22 are objected to because of the following informalities: The claims would be clearer if in the first instance where acronyms are used, said

acronym is first spelled out in full, followed by the abbreviation in parenthesis. Thus, for claim 4, (hGH) should follow after 'human growth hormone'; claim 8 should have the IGF-1 acronym spelled out and in claim 9, the acronym AUC should be spelled out first. The remaining claims not specifically identified are included in this objection because they do not remedy the cited deficiencies. Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 2nd paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 7, 8, 10 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131

USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In each of the instant claims there is a recitation of a set of concentration ranges and a set of time ranges in claims 7, 8 and 10; and just a set of concentration ranges for claim 22 . Thus, for example in claim 7, the claim recites the broad recitation of an hGH crystal wherein a single administration to a mammal provides an *in vivo* hGH serum concentration in said mammal the concentration selected from the group consisting of: a) 0.3-2500 ng/ml; b) 0.5-1000 ng/ml and c) 1-100 ng/ml which is the narrower statement of the range/limitation; furthermore, for a time period of i) 0.5 hours to 40 days; ii) 0.5-10 days; iii) 0.5-7 days and iv) 0.5-1day post-administration. However, because multiple ranges are included in the same claim, there is no way to distinguish the metes and bounds of the claimed invention.

11. Claims 7, 8, 10, 18 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "about" is a relative term which renders the claim indefinite. The term "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term leaves the claims indefinite because there is no standard deviation for which to ascertain the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 4, 7-10 and 17-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polyarginine human growth hormone (hGH) crystals made from calcium-acetate hGH crystals, does not reasonably provide enablement for all polyarginine hGH crystals, and specifically any polyarginine hGH crystals with the stated serum concentrations in a mammal of 0.3 ng/ml-2500 ng/ml in a time period of 0.5-40 days or 50% bioavalibility compared with soluble hGH. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to polyarginine crystals of growth hormone and derivatives thereof (claims 4 and 17), and also polyarginine crystals which for example must have serum concentrations of 0.3 ng/ml-2500 ng/ml (claims 7, 8, 10) [0.1-100 ng/ml for claim 22] after administration in a mammal and in a time period of 0.5-40 days (claims 7, 8 and 10) or 50% bioavalibility compared with soluble hGH (claim 9), or polyarginine hGH crystal compositions with additional excipients. However, the specification *only* sufficiently describes one polyarginine hGH crystal which meets the limitations of the claims (Example21) and also which necessarily provides sufficient details and experimental data (see Tables 12, 13, 16-26) to ensure that a skilled artisan would not

have to perform undue experimentation in order to achieve the stated *in vivo* limitations. The specification is void of any other types of polyarginine hGH crystals, but yet the scope of the claimed invention is drawn to a any and every kind of polyarginine hGH crystals or derivatives thereof. It is sufficiently clear from the prior art that while human growth hormones have been successfully crystallized previously, that the variation of conditions from protein to protein is significantly different and the variation of particular "additives" or excipients can profoundly change the crystallization conditions as well as the *in vivo* functionality of the composition. What is successful for one growth hormone species (crystal or soluble) certainly is not for another species. Thus, a skilled artisan, in order to achieve that which falls within the metes and bounds of the instant invention, would be required to determine both *de novo* processes to achieve successful crystallization conditions and crystals for each different polyarginine hGH crystal and derivatives thereof (e.g. bovine growth hormone) and subsequently to test each one to make sure it possesses the dependent claim limitations of particular bioavailability, serum concentrations which last for a particular time post administration. In this case, the burden is seen as undue when the Wands analysis is considered.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed

invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant case, the quantity of experimentation would be considerable because the smallest change in *any* parameter in crystallizing a protein can have enormous consequences (e.g. temperature, salts, buffers, additional additives, different protein variants, etc.). Thus, it is not enough to have the crystallization conditions of a related/similar protein or 'native' protein. Rather, what would be required is precise instruction about how to make the protein crystal (*each and every one*) in order to avoid undue experimentation. However, there is no direction or guidance in the specification of how a skilled artisan might achieve polyarginine crystals of *all* growth hormone proteins and *all* derivatives thereof, the only example which sufficiently meets this burden is Example 21. The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily

work for a mutant or a protein complex even though they contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein complex) (see Weber, Overview of Crystallization Methods. Methods in Enzymology, 1997, Vol. 276, pp. 13-22). *At best*, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful for a single protein. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a fortuitous role in obtaining successful crystallization conditions despite the extremely high skill level of those in the art (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2). Furthermore, the prior art is of little assistance because there are so many different conditions which work for different growth hormones (see for example, US Patents, 4,816,568; 5,633,352; 5,667,808; 5,734,026; 5,780,599; 6,022,858 and 6,117,984 – cited on the IDS from 11 Jan. 2005) but which are sufficiently different than the claimed invention, one skilled in the art understanding the unpredictability of the art, would have no reason to expect that other growth hormones other than hGH and, perhaps met-hGH, would reasonably produce polyarginine crystals with the stated limitations of the dependent claims. Thus, when all things are considered and the Wands factors are treated on their merits, the claim is not enabled

because a great deal of undue experimentation would be expected and necessary in order to practice the full scope of claimed invention.

Written Description:

14. Claims 4, 7-10 and 17-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polyarginine crystals of human growth hormone and derivatives thereof and compositions containing the same, with specific limitations on the bioavailability, serum concentrations and how long the hGH lasts in the serum post-administration. The instant claims are drawn to a broad genus of any crystal of polyargnine hGH (claim 4) or one that is composition thereof with an additional excipient (claim 17). While the structure and function of a single species of said genera of polyarginine hGH crystals are disclosed in the specification, the common characteristics of that species that define said genera are not described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (Enzo Biochem 63 USPQ2d 1609 (CAFC 2002)).

The specification fully and adequately describes one species of polyarginine hGH crystals that are produced by a microbatch method that falls within the instant genera of crystals. Example 21(pp. 59-60) describes the precise hGH resuspension buffer and the exact crystallization conditions (30 mg/ml hGH, 1M Tris-HCL, pH 8.6, 50% PEG-6000 and 1M Ca-acetate; mixed gently at 15-33 °C for 12-16 hours); resuspend said Ca-hGH crystals in 5mM CaOac, 100 mM Tric-HCL, pH 8.6, 6% PEG-6000, and add plyarginine at a concentration of 4.2 mg/ml, or in a 5:1 (mg:mg) protein to polyarginine ratio). This Example sufficiently and fully describes a calcium-polyargnine hGH crystal, which furthermore, has been adequately and sufficiently been tested for its serum concentration, bioavailability and post administration time concentration post administration *in vivo*. However, this single species does not sufficiently describe the entire genus of polyarginine hGH crystals.

In general, for a species of crystal to be adequately described, the following must be adequately disclosed in the specification and the claims: (1) the composition of the

crystal (exact structural features of all molecules in the crystal must be described, including the protein/antibody (preferably a SEQ ID NO of all included residues) and any molecule bound to it) (2) the exact protein concentration and buffer the protein/antibody is in, (3) the exact temperature, buffers, salts, additives used for crystallization and 4) the technique used to obtain the crystal (e.g. vapor diffusion, microbatch, liquid-liquid diffusion, etc). The single species noted above has adequately met this burden. However, the process of obtaining the crystals which is encompassed by the breadth of the claims is not described. A singular chemical composition can crystallize differently based on the crystallization conditions and techniques used. For example, if a skilled artisan wants to crystallize hGH for structural studies, then the crystallization technique, buffer considerations, temperatures, etc. are likely going to very different than when said artisan is trying to crystallize a protein for therapeutic use because the overall objectives are so different and the quality and quantity of the crystals are important but different for each.

Based on the instant the specification, the chemical composition, the polyarginine hGH crystals and specific *in vivo* quality of the crystals produced encompassed by the breadth of the claims is unpredictable to one of skill in the art. Therefore, the claims drawn to the instant genera of hGH crystals are also not adequately described.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 4 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Cunningham et al. (US 5,849,535).

The claim is drawn to a polyarginine crystal of human growth hormone *or* a human growth hormone derivative (claim 4) and an excipient (claim 17). Cunningham et al. teach variants/derivatives of human growth hormone with several different amino acid substitutions (see claim 1) as well as polyethylene glycol derivitized proteins (see claims 2-5); a derivative hGH composition with an excipient is taught in column 25, line 24.

Thus, Cunningham et al. teach human growth hormone derivatives as stated in the instant claim.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claim 4 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 7, 9 and 10 of copending Application No. 11/169,956 (US 2006/0008532). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the many choices recited in the claims for what kind of protein is actually contained in the protein crystal of claim 1, and the many choices offered for the ionic compound the crystal is in complex with. Nonetheless, an obvious variation and choice of the many variations is a protein crystal of human growth hormone in complex with polyarginine which reads on instant claim 4.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

19. No claim is allowed. Applicants are encouraged to call the examiner for any queries or in order to facilitate prosecution of the instant Application.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.30am to 4.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber (AU 1653) or Kathleen Kerr (AU 1656) can be reached on 571-272-0925 and 571-272-0931, respectively. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN
26 July 2006

KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER